COGNITIVE PROFILE IN RENAL TRANSPLANT RECIPIENTS

Dissertation submitted to

THE TAMILNADU DR.MGR MEDICAL UNIVERSITY

in partial fulfillment of the requirements

for the award of the degree of

DM (NEUROLOGY) – BRANCH -1

MADRAS MEDICAL COLLEGE

THE TAMILNADU DR.MGR MEDICAL UNIVERSITY

CHENNAI

AUGUST 2014

CERTIFICATE

This is to certify that the dissertation entitled **"COGNITIVE PROFILE IN RENAL TRANSPLANT RECIPIENTS"** is a bonafide record of work done by **Dr.N.SHANKAR GANESH in** the Institute of Neurology, Rajiv Gandhi Government General Hospital & MADRAS MEDICAL COLLEGE, CHENNAI in partial fulfillment of the Tamilnadu Dr.MGR Medical University rules and regulations for the award of D.M. (NEUROLOGY) degree under my direct guidance and supervision during the academic year 2011-2014.

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DECLARATION

I solemnly declare that this dissertation titled **"COGNITIVE PROFILE IN RENAL TRANSPLANT RECIPIENTS"** is done by me in the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of **Prof. Dr. R.LAKSHMI NARASIMHAN, MD., DipNB., D.M., DipNB.,** Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of D.M. Neurology.

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ACKNOWLEDGEMENT

It gives me great pleasure to acknowledge all those who guided, encouraged and supported me in the successful completion of my dissertation.

First and foremost, I express my gratitude to, the **Dean Dr. R. VIMALA, MD.,** for having permitted me to carry out this dissertation work at Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai.

I am extremely thankful to **Prof. Dr. K. MAHESHWAR, M.ch.** Professor of Neurosurgery, Head of the department, Institute of Neurology, Rajiv Gandhi Government General Hospital, Chennai for his constant encouragement, valuable guidance and support.

I express my deep sense of gratitude and sincere thanks to our respected and beloved Chief **Prof. Dr. R.LAKSHMI NARASIMHAN, MD., DipNB., D.M., DipNB., Professor of Neurology,** Institute of Neurology, Rajiv Gandhi Government General Hospital, Chennai for his valuable suggestions, constant motivation, kind guidance and moral support without which this study would not have been possible.

I express my sincere thanks and gratitude to our Professors **Prof. Dr. K.Bhanu,Dip.NB.,D.M.,** P**rof.Dr.G.Sarala,MD.,DM., Prof.Dr.M.Balasubramanian,MD.,DM**., **Prof.Dr.V.Kamaraj,MD.,DM.,and Prof. Dr.S.GOPALAKRISHNAN, Professor of Nephrology** for their valuable suggestions and support.

I am extremely thankful to all my **Assistant Professors** for their valuable guidance and support.

I owe my sincere thanks to all the patients and the technical staff who participated in the study for their cooperation which made this study possible.

CONTENTS

ABSTRACT

"COGNITIVE PROFILE IN RENAL TRANSPLANT RECIPIENTS"

N.SHANKAR GANESH [1], PROF. DR. R.LAKSHMI NARASIMHAN, [2]
DR.S.GOPALAKRISHNAN, [3]

Aim; To study and analyze the cognitive status like attention, language, memory and lobar function in patients with chronic kidney disease before and after renal transplantation

❖ **Materials and methods;** This study was conducted from May 2012 to January 2014, Prospective study between May 2012 to January 2014, twenty five patients, **Exclusion Criteria:** Mentally retarded, Organic Psychosis, Patient on anti depression, had an absence of acute illness (e.g., metastatic cancer), neurological disease, and other major organ failure (e.g., end stage liver disease. Detailed history and neurological examination like mini mental state examination. Detailed lobar function, Addenbrooke's cognitive examination-revised scale.Alzheimer's disease Cooperative Study (ADAS) - Cognitive Behavior. Wescthler Memory Scale will be done.

Details regarding the treatment will be obtained from history and treatment records. Analysis by standard method; Chi-Square Tests, student T test.

Results; Among the cognitive function the executive function, Attention task, Anterograde memory, verbal fluency, and word recognition in memory function has been improved after renal transplant. . In memory function there is significant improvement in recall, Anterograde memory, verbal fluency, and word recognition after renal transplant, but there is no significant changes in the retrograde memory. No statically significant changes in language, the blood parameters are improved well.

Conclusion; even the some of the cognitive domain is improved the further study in large groups in various cognitive domains and long term follow-up to determine the cognitive improvement.

KEY words; ADAS score, renal transplant, cognitive level.

Author;1. Resident in neurology, 2.professor of neurology, 3.professor of nephrology.

INTRODUCTION

Renal disease is a gradually increasing common chronic illness affecting the middle and older adulthood. Chronic kidney disease affects 5-10% of the world population and is a universal health problem. When compared with the general population the prevalence of cognitive impairment is high in end stage renal disease (ESRD) [1,2]. The overwhelming of cognitive impairment in chronic kidney disease and patients undergoing haemodialysis is noticeable only in the recent years. Severe cognitive impairment is synonymous in comparison to dementia. DSM -V criteria duly states that dementia is a chronic cognitive impairment in two or more cognitive domains that substantially affects the daily function, representing a decline in the pre – morbid function and is not due to concomitant acute delirium. Though there is compromised cognition in patients undergoing dialysis, cumulative evidence shows that there is increased risk for cognitive difficulties in individuals even in the early course of the disease before the occurrence of renal failure. Having said that the cognitive performance following successful renal transplant is unclear, it is usually believed that the cognitive features return to pre-morbid levels after successful renal transplantation. Short screening tests such as Mini Mental State Examination [MMSE] [3]and 3MS –an adjunct of MMSE, which contains four added subtests, are applied to test cognitive impairment and a maximum

score of 100 points are given. On the whole these screening tests have limited sensitivity particularly for vascular cognitive impairment. So the prevalence of cognitive impairment in CKD [4,5] is still under estimated. In this study, the cognitive function in renal transplant recipient is assessed by various methods before and after [9 months] renal transplantation. The methods are:

1] Mini Mental State Examination [MMSE]

2] Higher mental functions and lobar functions

3] Addenbrooke's Cognitive Examination

4] Wescthler Memory Scale

5] Alzheimer's Disease Cooperative Study - ADAS Cognitive Behaviour

AIM OF THE STUDY

To study and analyze the cognitive status like attention, language, memory and lobar function in patients with chronic kidney disease before and after renal transplantation.

REVIEW OF LITERATURE

Chronic kidney disease fringes a range of multifarious patho physiologic processes related to abnormal renal functions and a progressive deterioration in glomerular filtration rate (GFR). Stages of CKD depend upon GFR which is represented in the tabulation below. (Table -1)

Table -1*:* Classification of Chronic Kidney Disease (CKD) [6]

Stage	GFR, mL/min per 1.73 m^2
0	>90[a]
1	≥90[b]
2	60–89
3	30–59
4	15–29
5	<15

a) With risk factors for CKD.

b) *With* demonstrated kidney damage (e.g., persistent proteinuria, abnormal urine sediment, abnormal blood and urine chemistry, abnormal image studies).

***Abbreviation**:* GFR, glomerular filtration rate.

Chronic renal failure (CRF) refers to the process of continuous, significant and irrevocable decrease in the number of nephrons which classically corresponds to the stages 3–5 of CKD. The term end-stage renal disease (ESRD) pertains to the stage of CKD in which there is accumulation of toxins, electrolytes and fluids that are normally excreted by the kidneys. The cumulative effect of these toxins results in uremic syndrome which is fatal. These uremic toxins are eliminated by Renal replacement therapy, using dialysis or renal transplant.

Estimation of Glomerular Filtration Rate (GFR) is essential for the interpretation of stages of CKD. Parameters used are age, sex, body weight, race, serum Creatinine. The equations recommended for the calculation of GFR is as follows :(table-2)

Table 2: Recommended Equations for Estimation of Glomerular Filtration Rate (GFR) Using Serum Creatinine Concentration (PCr), Age, Sex, Race and Body Weight [7,8]

1. Equation from the Modification of Diet in Renal Disease study*
   Estimated GFR (mL/min per 1.73 m^2) = $1.86 \times (P_{Cr})^{-1.154} \times (age)^{-0.203}$
   Multiply by 0.742 for women
   Multiply by 1.21 for African Americans
2. Cockcroft-Gault equation
   Estimated creatinine clearance (mL/min)
   $= \frac{(140 - age) \times body\ weight\ (kg)}{72 \times P_{Cr}\ (mg/dL)}$
   Multiply by 0.85 for women

Leading categories of Etiologies of CKD:

CKD being a universal health problem, several factors contribute to the aetiology of CKD (table-3). These factors vary according to different geographical region. Among those are five leading categories that account for more than 90% of CKD.

Table - 3: Leading Categories of Etiologies of CKD [9]

- Diabetic glomerular disease
- Glomerulonephritis
- Hypertensive nephropathy
  - Primary glomerulopathy with hypertension
  - Vascular and ischemic renal disease
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy

*Relative contribution of each category varies with geographic region.

CLINICAL ABNORMALITIES IN UREMIA [10]

Uraemia causes functional disturbances in all organ system producing various symptoms.

Fluid and Electrolyte Disturbances:

- Volume expansion (I)
- Hyponatremia (I)
- Hyperkalemia (I)
- Hyperphosphatemia (I)

Endocrine-metabolic disturbances:

- Secondary hyperparathyroidism (I or P)
- Hyperuricemia (I or P)
- Hypertriglyceridemia (I or P)
- Increased Lp(a) level (P)
- Decreased high-density lipoprotein level (P)
- Protein-energy malnutrition (I or P)
- Impaired growth and development (P)
- Infertility and sexual dysfunction (P)
- Amenorrhea (I/P)
- β2-Microglobulin–associated amyloidosis (P or D)

Neuromuscular disturbances:

- Fatigue (I)*b*

- Sleep disorders (P)
- Headache (P)
- Impaired mentation (I)*b*
- Lethargy (I)*b*
- Asterixis (I)
- Muscular irritability
- Peripheral neuropathy (I or P
- Restless legs syndrome (I or P)
- Myoclonus (I)
- Seizures (I or P)
- Coma (I)
- Muscle cramps (P or D)
- Dialysis disequilibrium syndrome (D)
- Myopathy (P or D)

Cardiovascular and Pulmonary disturbances:

- Arterial hypertension (I or P)
- Accelerated atherosclerosis (P or D)
- Hypotension and arrhythmias (D)

- Vascular calcification (P or D)

Dermatologic disturbances

Gastrointestinal disturbances

Hematologic and immunologic disturbances

Response to treatment modalities

a) After successful renal transplant there is complete reversal of all the above mentioned abnormalities.

There is variable response to haemodialysis or peritoneal dialysis.

(I) Symbolizes an optimal program of dialysis and related therapy.

(P) Indicates an abnormality that lasts, despite of an optimal program.

(D) Signifies an abnormality that develops after the commencement of dialysis.

b). Refines with erythropoietin and dialysis:

Abbreviation: LP (a), lipoprotein A.

CHARACTERISTICS OF COGNITIVE IMPAIRMENT IN CKD

There is an increased association of end-stage renal disease (ESRD) with cognitive impairment. Recent data[11] suggests that the probability of developing cognitive impairment and dementia is high among patients with

CKD (irrespective of the stage) than patients without CKD .There is a registered history of cognitive impairment only in 3% of patients. So further neuropsychological testing's were done and proved that a higher prevalence [12] of 87% of patients were subjected with mild to severe degree of cognitive impairment.

Possible causes of cognitive impairment in patients with CKD

1) Vascular Hypothesis
2) Neurodegenerative Hypothesis

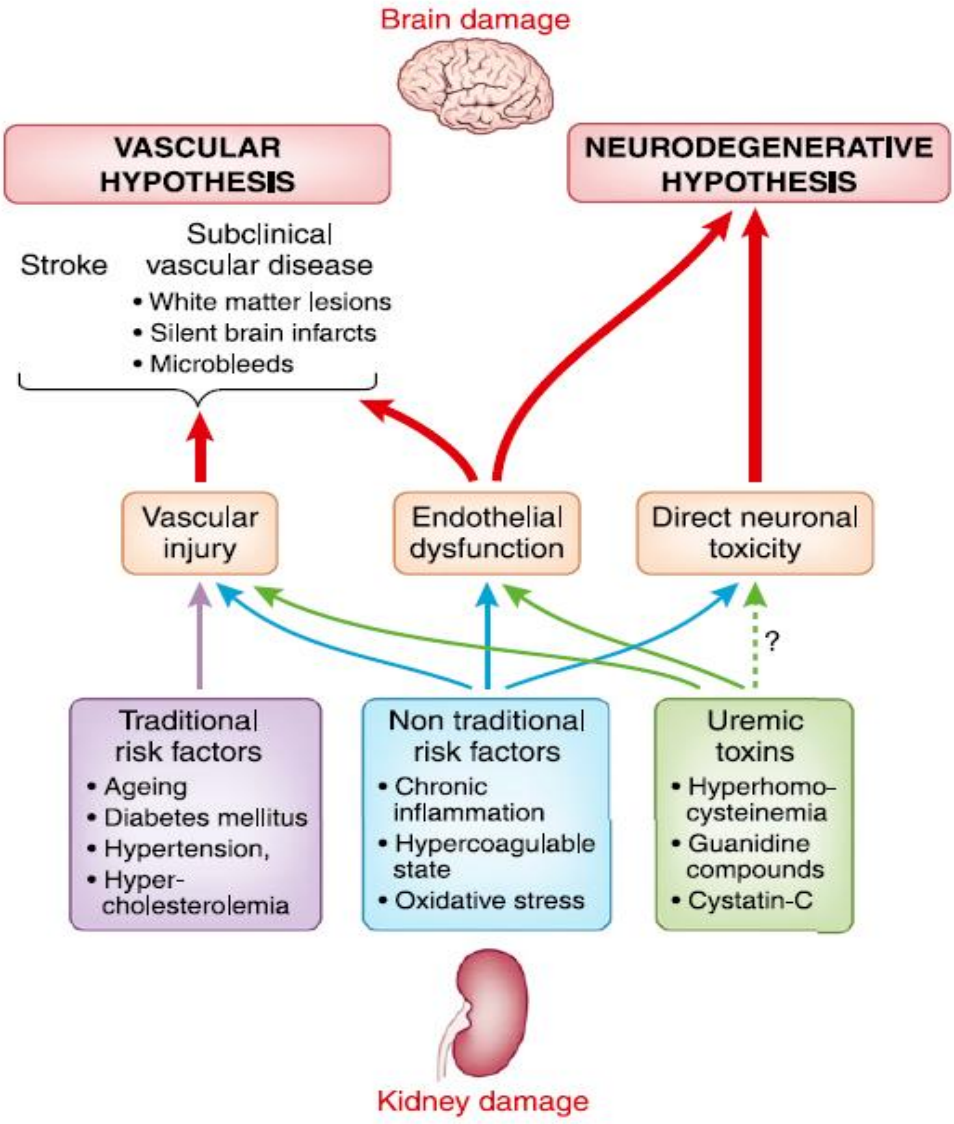


Illustration of the Probable causes of cognitive impairment in CKD patients (figure-2)

1) Vascular Hypothesis of cognitive impairment in patients with CKD.

According to this hypothesis the brain and kidneys share many common features like anatomic and vaso regulation. The end organs with low resistance are exposed to a larger volume of blood flow and are thus subjected to vascular damage [13]. Hence the Tran cranial Doppler Ultrasonography is used for the evaluation of impaired cerebral hemodynamic [14]. This provides fascinating information on the link between cognitive impairment and altered cerebro - vascular hemodynamic. Previous Tran cranial Doppler Ultrasonography studies revealed a positive correlation between cognitive impairment and impaired hemodynamic, proposing that the micro vascular damage subscribes to the changes in cognitive that are identified in the early levels of dementia [15,16].

Arterial hypertension being a major vascular risk factor contributes to cerebrovascular disease which plays an extensive role in the pathogenesis of impairment in cognitive functions in patients with CKD. This explains the coalition between CKD and Cerebrovascular disease [17,18]. Arterial hypertension is highly prevalent in patients with CKD than in others.

Furthermore, the contribution of cerebral vascular lesions to cognitive impairment in CKD patients is supported by various hypotheses:

1) It is suggested that the cause of cognitive impairment is more due to vascular disease when compared to Alzheimer's disease .An imparted data from the 3C study favours this hypothesis. The study showed that the faster decline in eGFR (follow-up during first 4-year period-0.4 ml/min per 1.73 m2) was proportional to global cognitive dysfunction and an episode of dementia comprising vascular component.

2) The contribution is also supported by the notable decline in executive functions and the psychomotor speed similar to the picture in stroke [17].

3) The pattern of cognitive disorders.

However, neuropathology studies revealed a wider dysfunction in cognition exists among patients suffering from small-vessel cerebrovascular disease including memory deficits.

There is also a link between cognitive impairment and non-traditional vascular risk factors like inflammation, oxidative stress, and Hypercoagulable states and hyperhomocysteinemia [19]. These factors speed up the process of atherosclerosis and vascular endothelial dysfunction [20,21]. These twin factors are associated with risk of dementia.

HYPERHOMOCYSTEINEMIA AND COGNITIVE IMPAIRMENT

Hyperhomocysteinemia is seen in 10% of general population and 85% in dialysis patient [23]. According to a prospective cohort study, plasma homocysteine was found to be an independent risk factor for dementia [24].

Elevated homocysteine levels leads to Cognitive impairment and this is explained by various mechanisms.

1) Direct prothrombotic effect of hyperhomocysteinemia on the vascular system affects both large and small sized vessels [25]. Increased levels of homocysteine provoke a direct injury to the endothelium or stimulate an endothelial inflammatory response resulting in WML and its progression [26, 27].

Hyperhomocysteinemia impairs neuronal pathways by direct, neurotoxic effect either by conversion into homocysteic acid or activating N-methyl-D–aspartate receptor which leads to cell death [28] .

2) As per clinical studies there is an increased risk for Alzheimer disease [29] in hyperhomocysteinemia. However reducing the levels of homocysteine in dementia patients does not lower the global cognitive decline [30] .

2) NEURODEGENERATIVE HYPOTHESIS OF COGNITIVE IMPAIRMENT

There is high frequency of vasulopathy-related cognitive disorders in CKD patients but this can only be partly explained through brain abnormalities and vascular risk factors. So, other disease mechanisms are also involved.

1) Chronic hypertension and other vascular risk factors share an increased risk for Alzheimer disease [31].

Conversely, the results of clinical trials and observational studies suggest that anti-hypertensive drugs lower the age-related dementia and cognitive decline, though longitudinal studies provide inconsistent findings [32].

The Rotterdam study conducted in 2001 showed that there was only a lower risk for vascular dementia associated with anti hypertensive treatment. Another study Syst-Eur (the systolic hypertension in Europe) and Syst-Eur 2 trials showed significant 50% reduction in the incidence of neurodegenerative and vascular dementia with anti hypertensive treatment.

The studies [33] conducted during the past decade focused on the observation that the BP lowering activity of various anti hypertensive drugs had no correlation with the beneficial effects in preventing cognitive decline and dementia.

It has been suggested that Angiotensin Converting Enzyme (ACE) inhibitors might have adverse effect on cognition because ACE mediated conversion of Ab42 into Ab40.

The Ab40 which is less amyloidogenic and also less toxic. Instead of ACE inhibitors the use of Angiotensin AT1-receptor blockers might endeavour a protective effect on cognition by activating AT2-receptors.

Furthermore, Uremic toxin accumulation may induce a cerebral endothelial dysfunction and thus contributes to cognitive disorders in patients with CKD [34]. Several Uremic toxins are implicated in the pathogenesis of cognitive impairment. However, it is still a dilemma that uremic toxins lead to cognitive impairment. DeDeyn et al reported that levels of some guanidine compounds such as guanidine, methyl guanidine, Creatinine and guanidinosuccinic acid in the brain and cerebrospinal fluid are substantially elevated in uremic patients. High toxin concentration (up to 10 fold rise in CKD patients than in control) were found in the brain regions such as thalamus, cerebral cortex and mammillary bodies that plays a determinant role in

Cognition [35]. The involvement of uremic guanidine compounds may be direct or indirect.

Studies in animals revealed that these guanidine compounds are neuroexcitatory agents and have convulsant activities. It can also have an indirect effect by favouring the elevation of serum homocysteine. Finally, Yaffe et al projected that community-resident elderly individuals who have increased levels of systatin-C (which is an inhibitor of cysteine proteases that binds with b-amyloid in the brain of Alzheimer disease patients) were found to have lower cognitive test scores and even after adjustment of vascular risk factors experienced a fall in cognitive function during a follow-up period of 7 years. In spite of the absence of MRI brain data's, cystatin-C produces a direct effect on risk of developing Alzheimer disease.

BRAIN IMAGING IN CKD PATIENTS

Clinically evident stroke and subclinical cerebrovascular disease in patients with CKD

A high prevalence of stroke is seen in patients with CKD.As per the U.S. Renal Data System, the prevalence of stroke among CKD patients are categorized as follows considering the age, sex and race

17% -Long term haemodialysis patients

10% -Patients with mild to moderate CKD

4% -General population without CKD

The risk of dementia is doubled in both CKD and non-CKD populations with a previous history of stroke.

Moreover, there is increased prevalence of subclinical cerebrovascular disease in CKD patients and manifests as silent brain infarcts, white matter lesions (WMLs), and cerebral infarcts with absent clinical symptoms and detected only by brain lesions with micro bleeds. Brain lesions in patients with CKD were first described in (CT) Computed Tomography-based studies .Passer et al reported over three decades that there was a prevalence of cerebral atrophy in CKD patients who underwent long term dialysis. It was proved that the lesions were prominent in the frontal lobes in such patients after correlation with duration of haemodialysis [36,37].

SBIs in CKD

Other risk factors have also been reported for cerebro vascular diseases like SBIs. Cusmano and Savazzi reported that around 10% of patients with CKD who were on haemodialysis had evidence of SBIs.

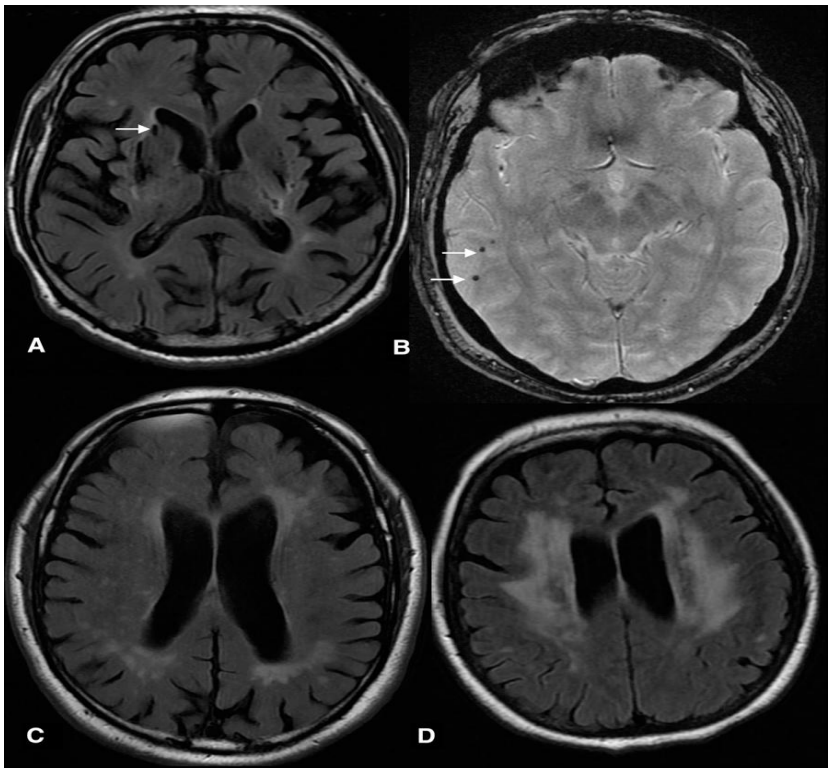
At recent times it was found that a strong bond existed between eGFR and calcification of intracranial arteries in patients admitted with stroke or any other non vascular neuro logical disorders. There is an active and accelerated

process of vascular calcification in patients with CKD.MRI is largely used to detect subclinical manifestations of Cerebrovascular damage in these patients .

The prevalence of SBIs is 8%-28% in normal individuals whereas it is 50% in advanced renal failure patients. SBIs are amalgamated with a higher incidence with stroke, incident dementia and decrease in cognitive function in CKD patients. The progressive worsening of GFR in patients with CKD revealed that SBI was an independent prognostic factor as illustrated in a prospective cohort study.

WML in CKD

There is increased prevalence of WML [38,39] (up to 70%) in patients with stroke and in CKD patients.WMLs also indicate arteriosclerosis. Similar to SBIs =WMLs are also associated with high risk for dementia and stroke and have also proved to be fatal. Cross-sectional studies done on general population proved a strong link between volume and lesions of white matter with eGFR. In a multivariate statistical analysis, Martinez –Vea et al failed to prove the association between WMLs and vascular nephropathy. This absence puts forward the fact that increased number of WMLs in renal failure patients signifies systemic vascular disease.Sub Clinical Brain Lesion in CKD Imaging: (figure-3)



A) Magnetic resonance imaging (MRI) in axial fluid – attenuated inversion recovery showing silent brain lacunars infarct (arrow).

B) Gradient – echo MRI imaging sequence showing micro bleed in multiple area located in right cerebral hemisphere (small foci of hypo intensity, arrow)

C) Moderate & (D) Severe white matter lesions in the area of centrum ovale.

MATERIALS AND METHODS

This study was conducted from May 2012 to January 2014. Patients were taken from department of nephrology in Rajiv Gandhi Government General hospital those who were enrolled for Renal Transplantation and undergone renal replacement replacement therapy. They were enrolled in this study after getting a written consent to analyses the cognitive status in chronic kidney disease patient before and after renal transplant, (6 to 9 months after renal transplant.

Design of the study duration of study:

Prospective study between May 2012 to January 2014, twenty five patients.

Material/ selection of subjects:

- 1. Those who are admitted in nephrology ward for renal transplant between 10-60 years of age.

Exclusion Criteria:

- Mentally retarded
- Organic Psychosis
- Patient on anti depression

- ❖ Had an absence of acute illness (e.g., metastatic cancer), neurological disease, and other major organ failure (e.g., end stage liver disease).

Methods/ Analysis:

- ❖ Detailed history and neurological examination like mini mental state examination.
- ❖ Detailed lobar function.
- ❖ Addenbrooke's cognitive examination-revised scale.
- ❖ Alzheimer's disease Cooperative Study (ADAS) - Cognitive Behavior.
- ❖ Wescthler Memory Scale will be done.

Details regarding the treatment will be obtained from history and treatment records. Analysis by standard method; Chi-Square Tests, student T test.

Assessment of Parameter:

The following clinical assessment will be made before and after renal transplant surgery.

- ❖ Attention
- ❖ Language

- Memory
- Detailed lobar function.
- Renal parameter, Blood pressure, heamoglbulin.

OBSERVATION AND RESULTS

Totally 25 patients were enrolled in this study after getting a written consent to analyze the cognitive status in chronic kidney disease patient before and after renal transplant, (6 to 9 months after renal transplant)

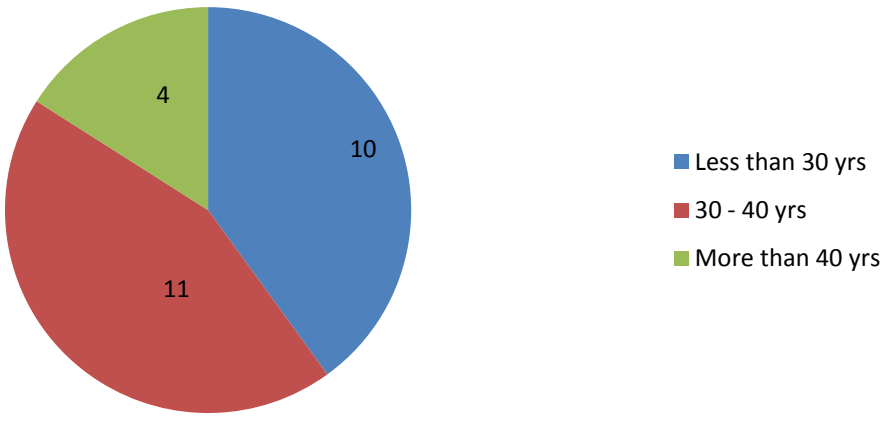
1. **Age Distribution**: The minimum age enrolled was 17 years and maximum age was 49 years. Less than 30 years were 10 in numbers 30 – 40 years 11 in numbers and more than 40 years were 23 in numbers. (Table-4, 5, Figure-4).

Table 4

Age in Years	N	Minimum	Maximum	Mean
	25	**17**	**49**	**32.52**

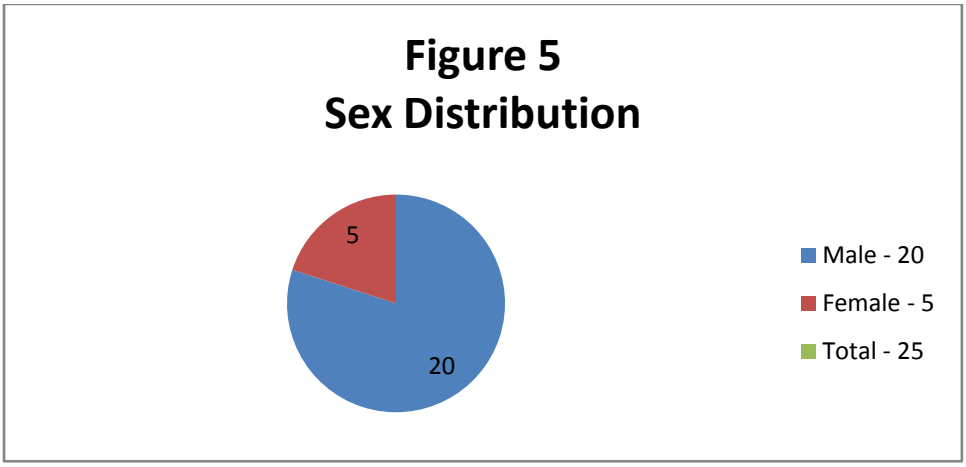
Table 5	
Age	**No. of patients**
< 30 years	**10**
30 to 40 years	**11**
>40 years	**4**

Figure 4
Age Distribution



2. **Sex Distribution**: In this study, out of 25patients 20 (80%) were males and 5(20%) were females (Table-6 and Figure-5).

Table 6				
Sex Distribution		**Frequency**	**Percent**	**Valid Percent**
	Male	**20**	**80.0**	**80.0**
	Female	**5**	**20.0**	**20.0**
	Total	**25**	**100.0**	**100.0**

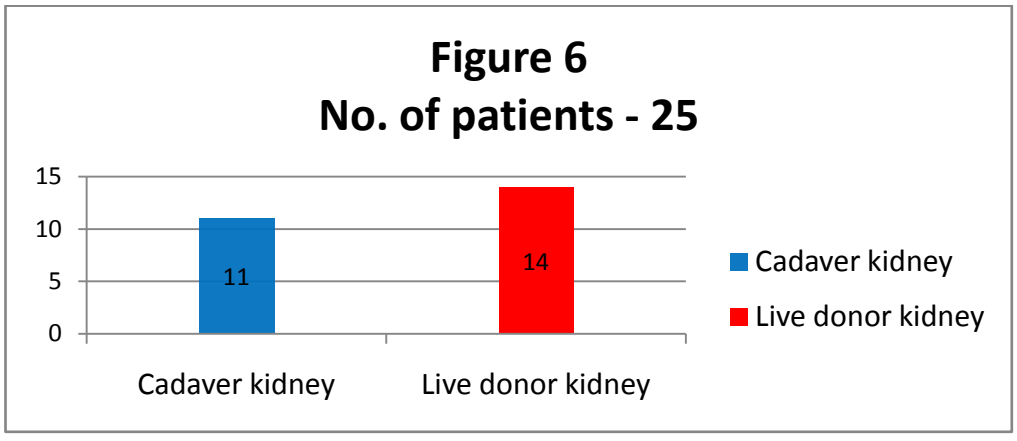


3. **Kidney Donor**:

Total number of patients is 25, cadaveric kidney was used in 11 patients (44%) and live donor kidney was used in 14 patients (56%).

(Table-7 and Figure-6).

Table 7		
Kidney Donor	**Frequency**	**Percent**
Cadaver	**11**	**44.0**
Live	**14**	**56.0**
Total	**25**	**100.0**

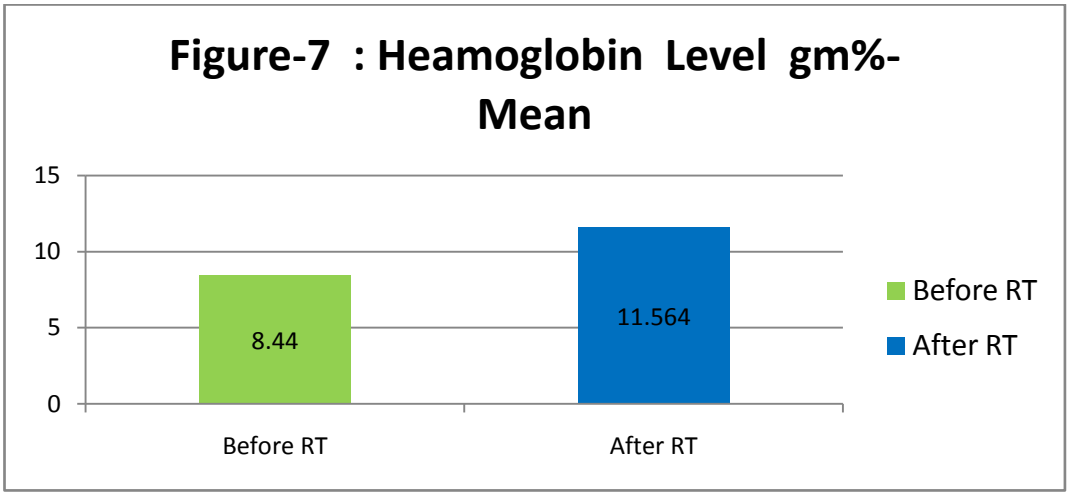


4. **Haemoglobin Level** - Before and after in transplant (gm %)

The mean Hb before RT was 8.44 and some of the patients were received injection Erythropoietin before surgery. The mean Hb after RT was 11.564 and there is significant p value (0.000) (Table-8and Figure-7).

Table -8

Haemoglobin Level		**Mean**	**N**	**Std. Deviation**	**P value**
1	**Haemoglobin(%) before RT**	**8.440**	**25**	**.3291**	**0.000**
2	**Haemoglobin(%) after RT**	**11.564**	**25**	**.7799**	



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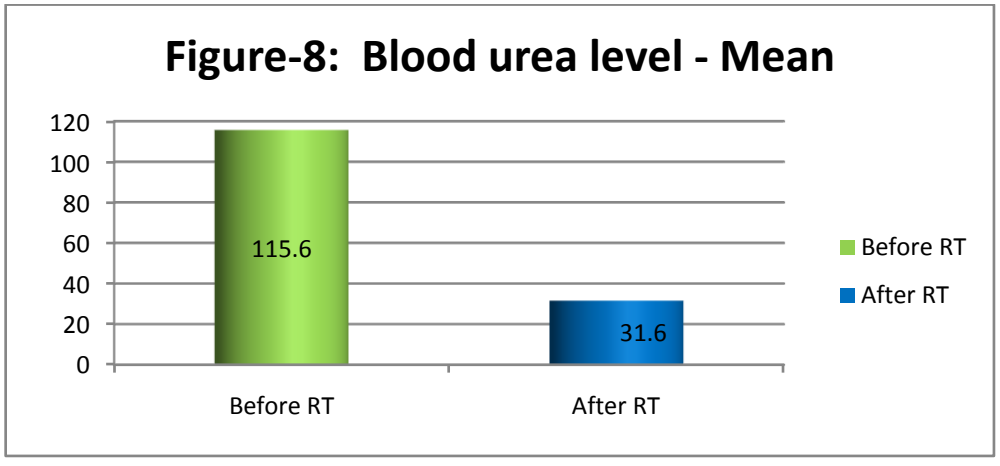
5. **Blood Urea Level** - Before & After RT

The mean blood urea level before RT was 115.60 and the mean blood urea level after RT was 31.60 there is significant p value(0.000) was noted (Table-9 and Figure-8).

Table-9

Blood urea level (mg %)		Mean	N	Std.Deviation	P value
1	Blood urea before RT(mgs)	115.600	25	21.5948	0.000
2	Blood urea after RT(mgs)	31.600	25	6.4291	



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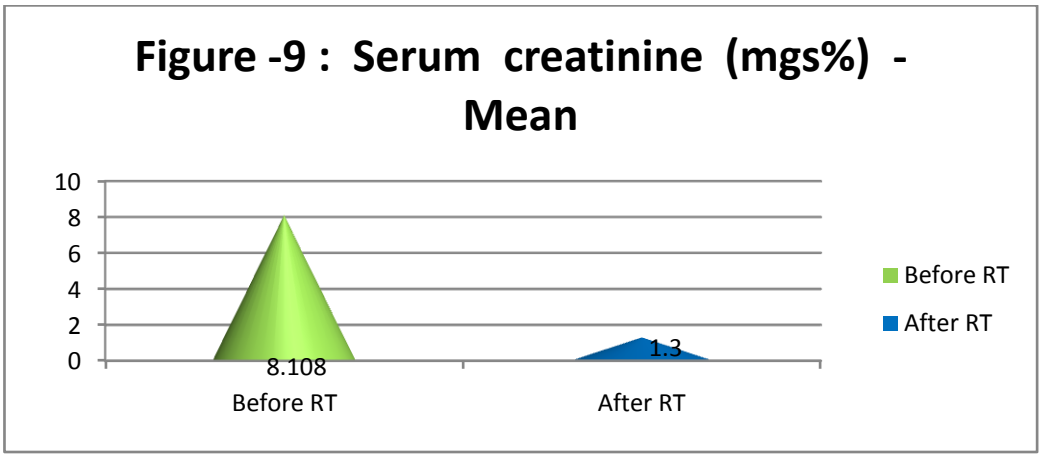
6. **Serum Creatinine** – Before & After RT

The mean serum Creatinine level before RT was 8.108 and the mean serum creatinine level after RT was 1.300 and there is significant p value(0.000) was noted . (Table-10 and Figure-9).

Table-10

Serum Creatine level (mg %)		Mean	N	Std.Deviation	P value
1	Serum Creatine level before RT	8.108	25	1.7628	0.000
2	Serum Creatine level after RT	1.300	25	0.3227	

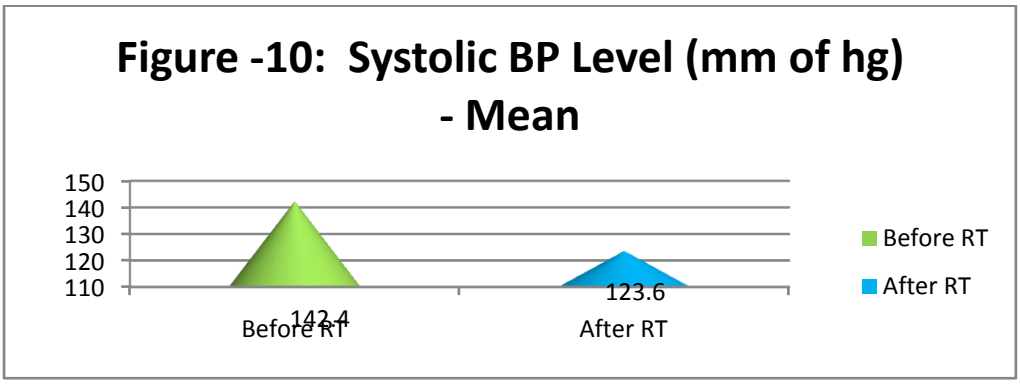


7. **Systolic BP** – Before & After RT :

The mean systolic BP level before RT was 142.40 and the mean systolic BP level after RT was 123.6 and there is significant p value(0.000) was noted. (Table-11 and Figure-10).

Table -11

Systolic BP level (mm of hg)		Mean	N	Std.Deviation	P value
1	Systolic BP level before RT	142.40	25	31.262	0.005
2	Serum Creatine level after RT	123.60	25	10.755	

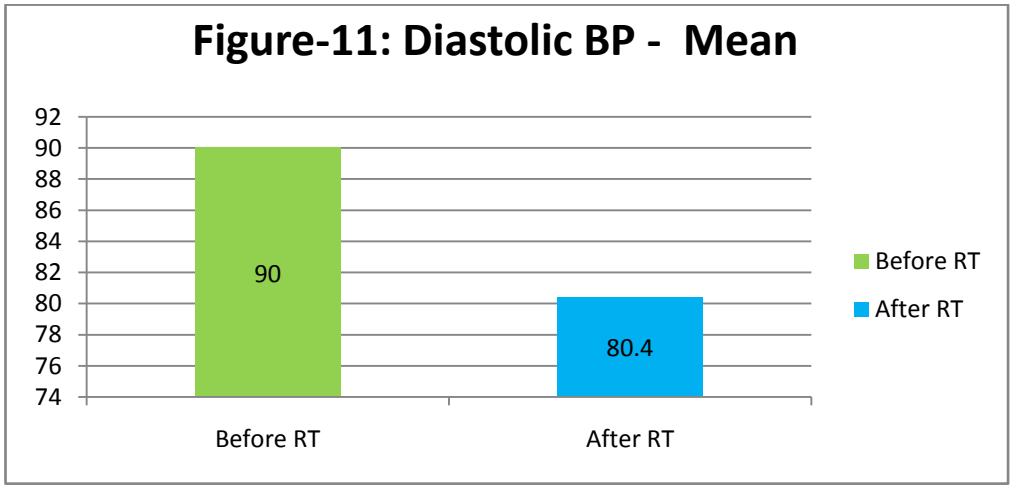


8**. Diastolic BP** – Before & After RT:

The mean diastolic BP level before RT was 90 and the mean diastolic BP level after RT was 80.40 and there is significant p value (0.000) was noted. (Table-12 and Figure-11)

Table-12

Diastolic BP level (mm of hg)		Mean	N	Std.Deviation	P value
1	Diastolic BP level before RT	90	25	9.129	0.000
2	Diastolic BP level after RT	80.40	25	5.385	

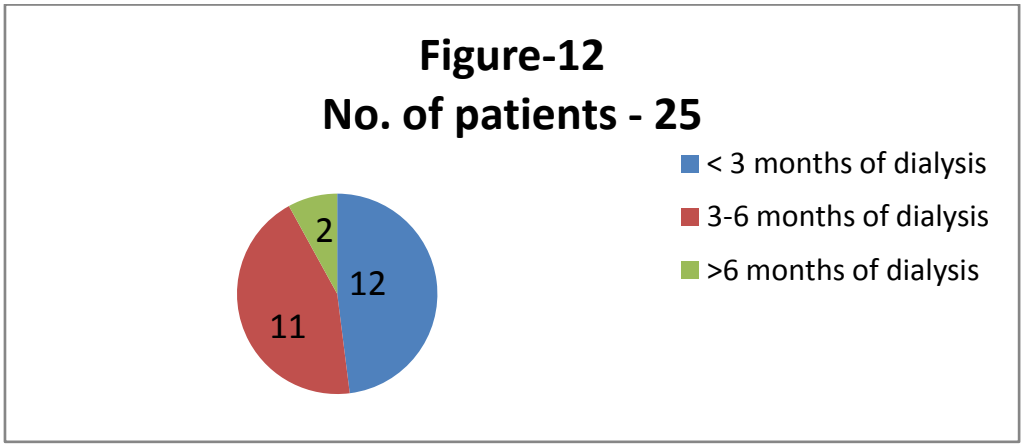


9 .**Duration of Dialysis before RT (in months)**

The duration of dialysis varied from 1 month to 10 months depends upon the availability of kidney donor. (Table-13 and Figure-12).

Table-13

Period of dialysis		Frequency	Percent
	< 3	12	48.0
	3-6	11	44.0
	> 6	2	8.0
	Total	25	100.0

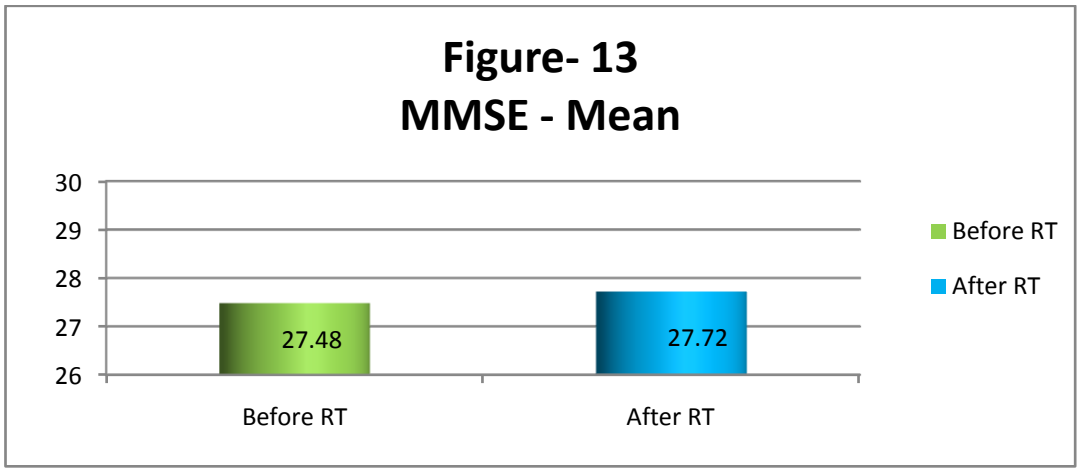


10. **Mini Mental State Examination (MMSE):**

Mini mental State Examination (MMSE) was conducted in all patients before and after RT and the mean difference was not statistically significant. (Table-14 and Figure-13).

Table-14

MMSE		Mean	N	Std. Deviation	P Value
	MMSE before RT maximum score 30	27.48	25	1.262	.110
	MMSE after RT maximum score 30	27.72	25	1.021	



11.**Attention & Orientation:**

The attention and orientation task was performed with ADAS scoring there was significant mean value which was statistically significant (Table-15).

Table-15

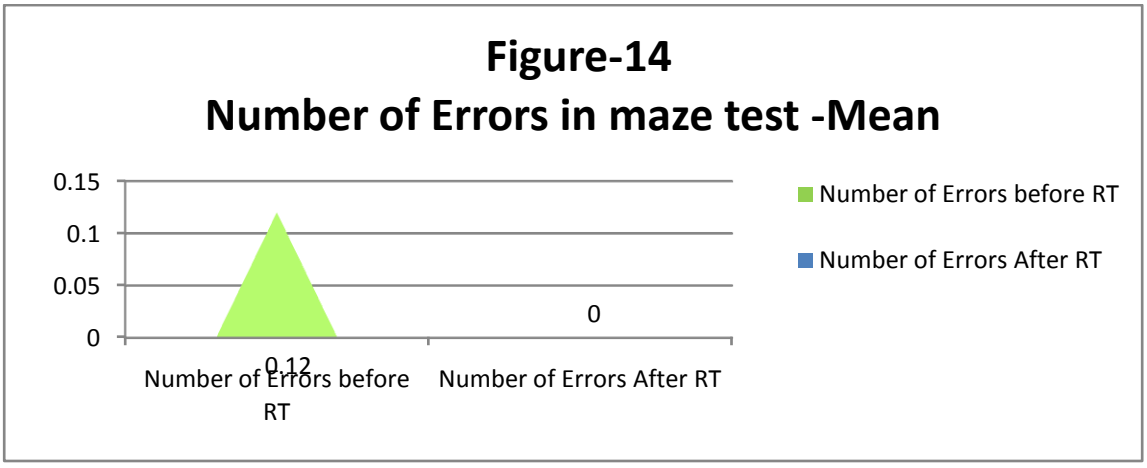
Attention & Orientation		Mean	N	Std. Deviation	P value
	Attention & Orientation - 15 pts before RT	13.48	25	.586	**0.000**
	Attention & Orientation - 15 pts after RT	13.88	25	.526	

12. **Number of Errors in Maze Test:**

The maze test was used as **Executive Function** to test the sequence of test and time of completion, there is significant p value was noted in number of error and time of completion. (Table-16 and Figure-14).

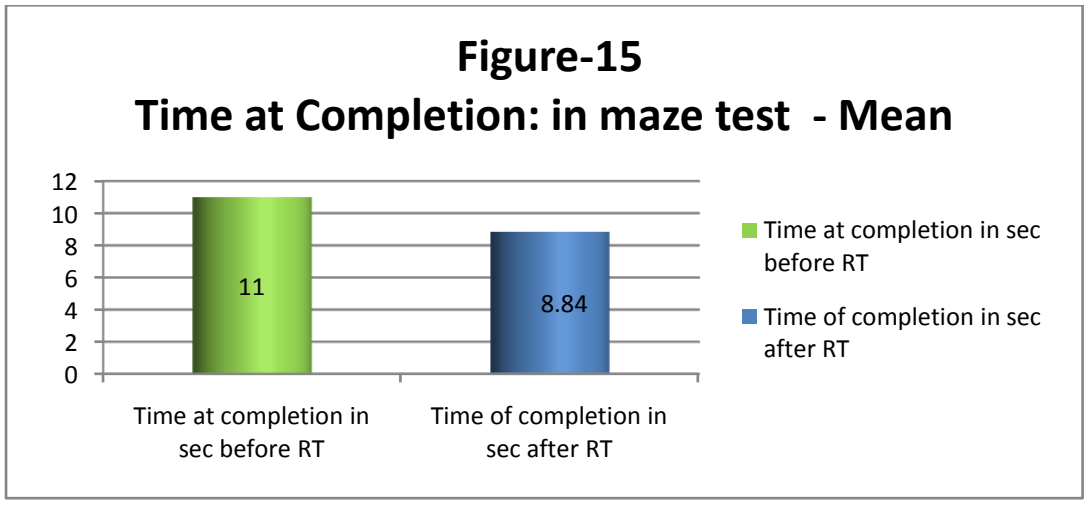
Table-16

Number of Errors		Mean	N	Std. Deviation	P value
	Number of Errors before RT	.12	25	.332	**0.001**
	Number of Errors after RT	.00	25	.000	



13.**Time at Completion in maze test**: (Table-17 and Figure-15).

Table-17				
Time at completion	Mean	N	Std. Deviation	P value
Time at completion in sec before RT	11.00	25	1.528	**0.000**
Time of completion in sec after RT	8.84	25	1.375	



14**. Constructional Praxis Before RT and After RT :** Chi-Square Tests

The constructional praxis was tested with circle. Two overlapping rectangles Rhombus Cube and there is significant improvement noted with constructional praxis before and after RT was noted. (Table-18).

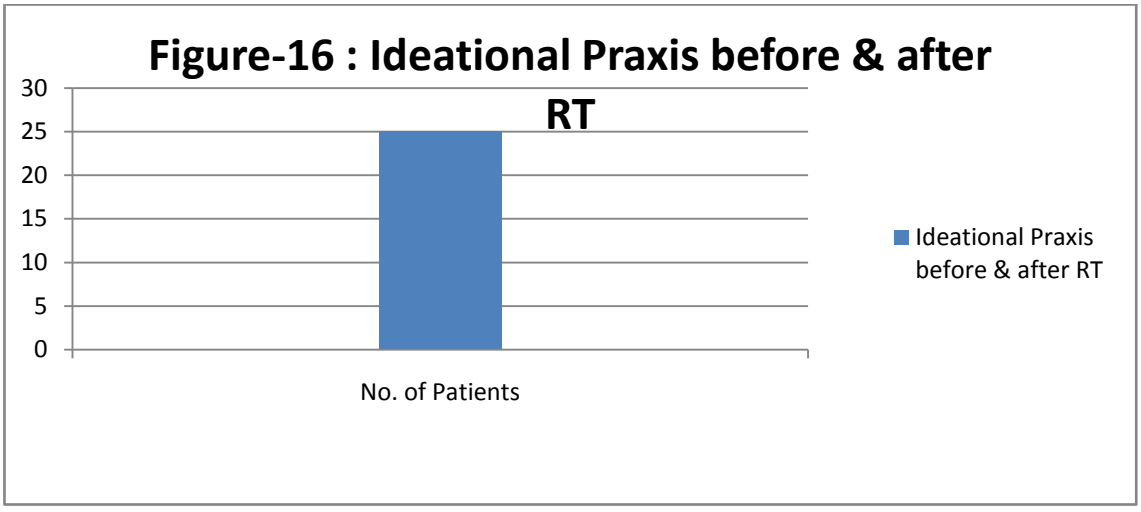
Table-18						
			Constructional Praxis after RT		Total	P value
			Normal	Abnormal		
Constructional Praxis before RT	Normal	Count	20	0	20	**0.000**
		% within Constructional Praxis before RT	100.0%	.0%	100.0%	
		% within Constructional Praxis after RT	90.9%	.0%	80.0%	
	Abnormal	Count	2	3	5	
		% within Constructional Praxis before RT	40.0%	60.0%	100.0%	
		% within Constructional Praxis after RT	9.1%	100.0%	20.0%	
Total		Count	22	3	25	
		% within Constructional Praxis before RT	88.0%	12.0%	100.0%	
		% within Constructional Praxis after RT	100.0%	100.0%	100.0%	

15. Ideational Praxis Before & After RT:

There is no statistically significant ideational praxis noted before and after RT. (Table-19 and Figure-16).

Table-19

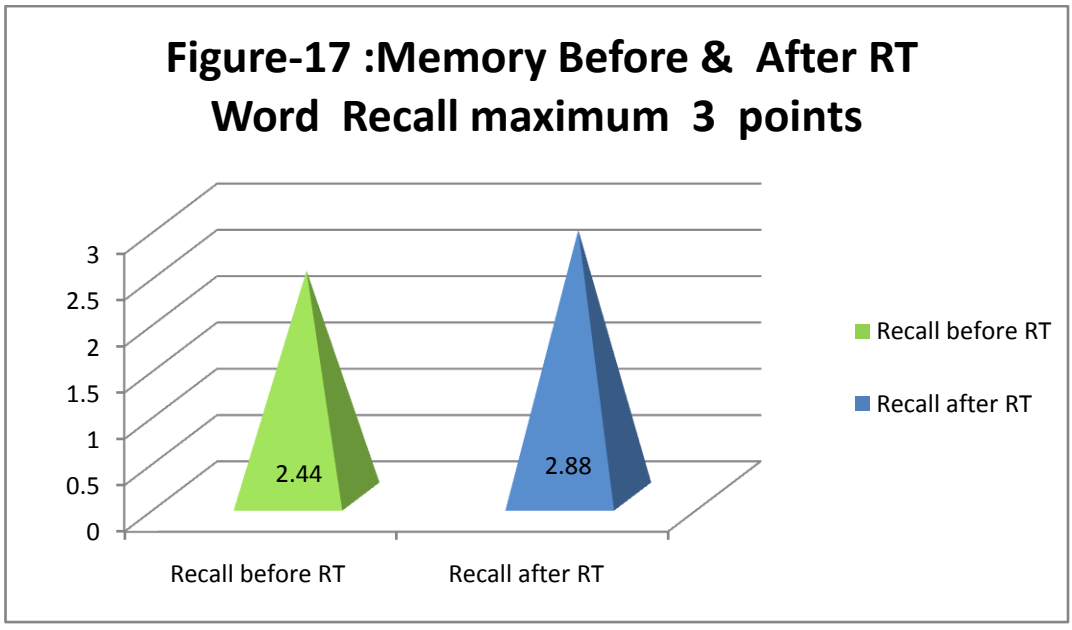
Ideational Praxis	Frequency	Percent	Valid Percent	Cumulative Percent
Normal	25	100.0	100.0	100.0



16. **Memory Testing Before & After RT:**

Memory was tested with following test. There is significant p value noted in recall test. (Table-20and Figure-17).

Table-20					
Recall		Mean	N	Std. Deviation	P Value
	Recall before RT max 3 points	2.44	25	.651	**0.001**
	Recall after RT max 3 points	2.80	25	.408	

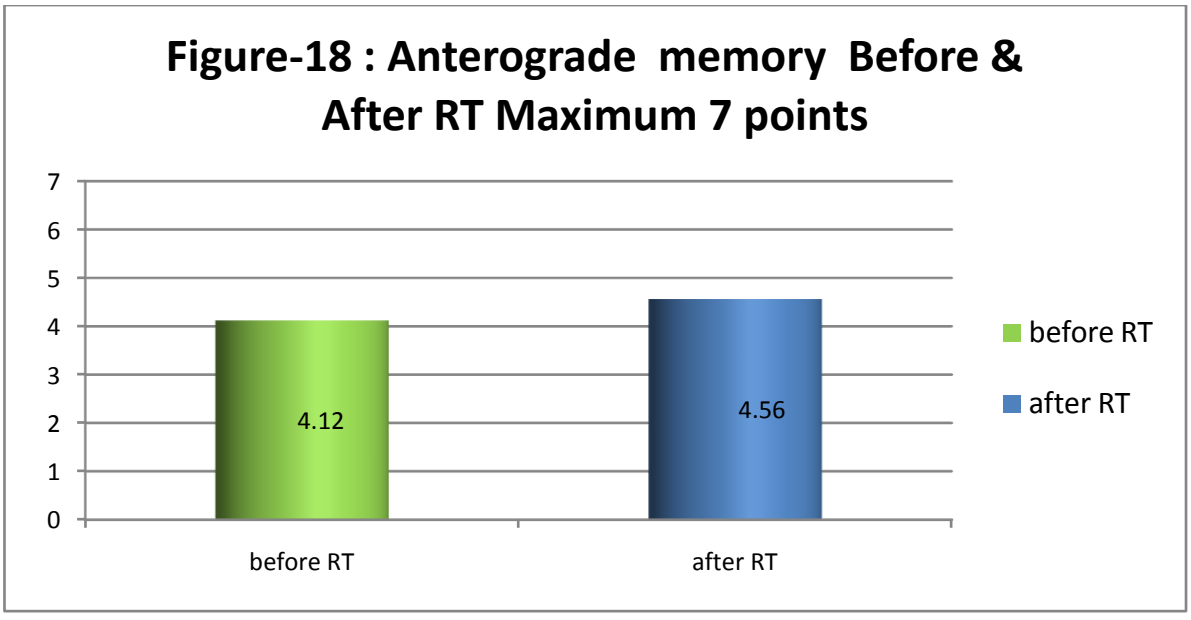


17. **Anterograde Memory Before & After RT:**

Memory was tested with a name and address and ask them to repeat the words, significant p value was noted after renal transplantation.

(Table-21 and Figure-18)

Table-21					
		Mean	N	Std. Deviation	P value
	Anterograde max points = 7 before RT	4.12	25	.726	.
	Anterograde max points = 7 after RT	4.56	25	.768	**0.000**



18. **Delayed Recall Before & After RT:**

Delayed memory was tested with a name and address and ask them to repeat the words, significant p value was noted after renal transplantation. (Table-22).

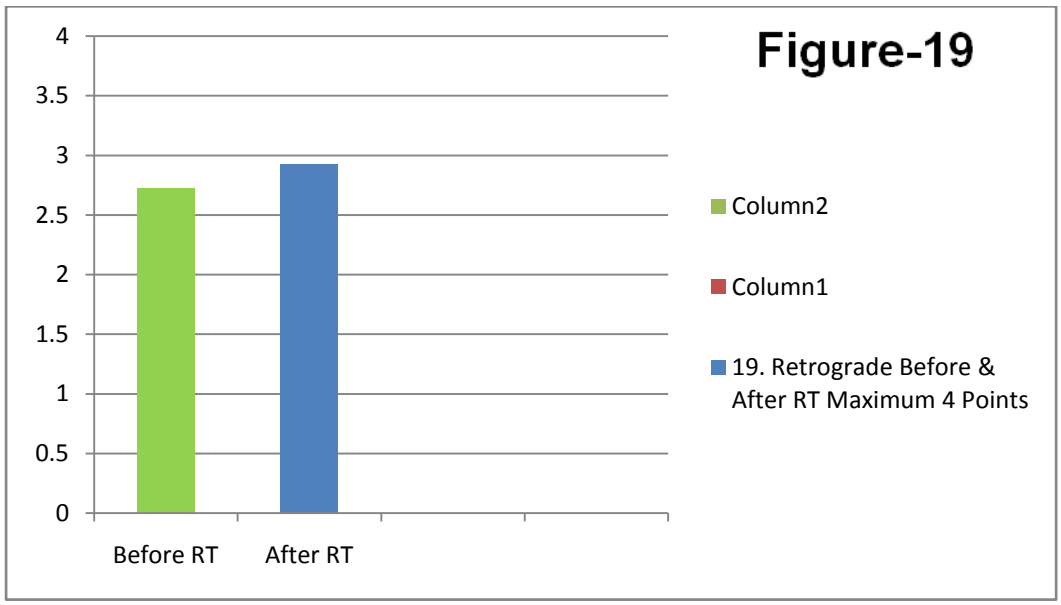
Table-22					
Delayed Recall		Mean	N	Std. Deviation	P Value
	Delayed Recall max 7 points before RT	3.32	25	.900	**0.000**
	Delayed recall after RT	3.80	25	.913	

19. **Retrograde Before & After RT:**

There is no significant p value noted when tested with retrograde memory (name of the chief minister or prime minister. (Table-23 & Figure-19).

Table-23

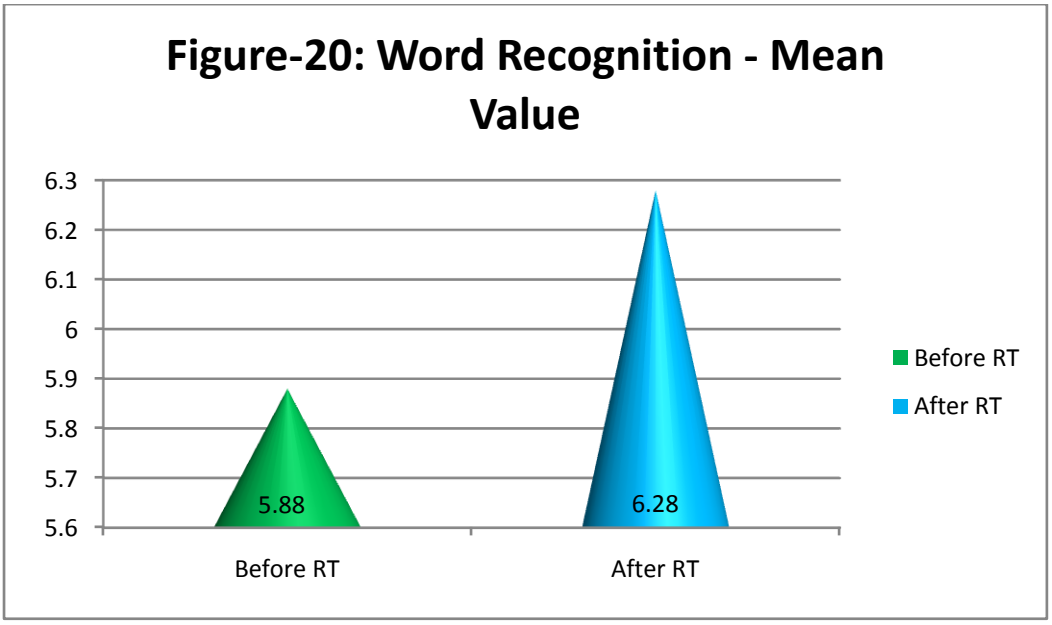
		Mean	N	Std. Deviation	P Value
	Retrograde max 4 points before RT	2.72	25	.843	0.022
	Retrograde max 4 points after RT	2.92	25	.759	



20. **Word Recognition Before & After RT:**

Word recognition was tested with 10 words and noted significant p value noted after RT. (Table-24 and Figure-20).

Table-24					
Word Recognition		Mean	N	Std. Deviation	P Value
	Word Recognition before RT"	5.88	25	1.013	0.001
	Word Recognition after RT"	6.28	25	1.137	

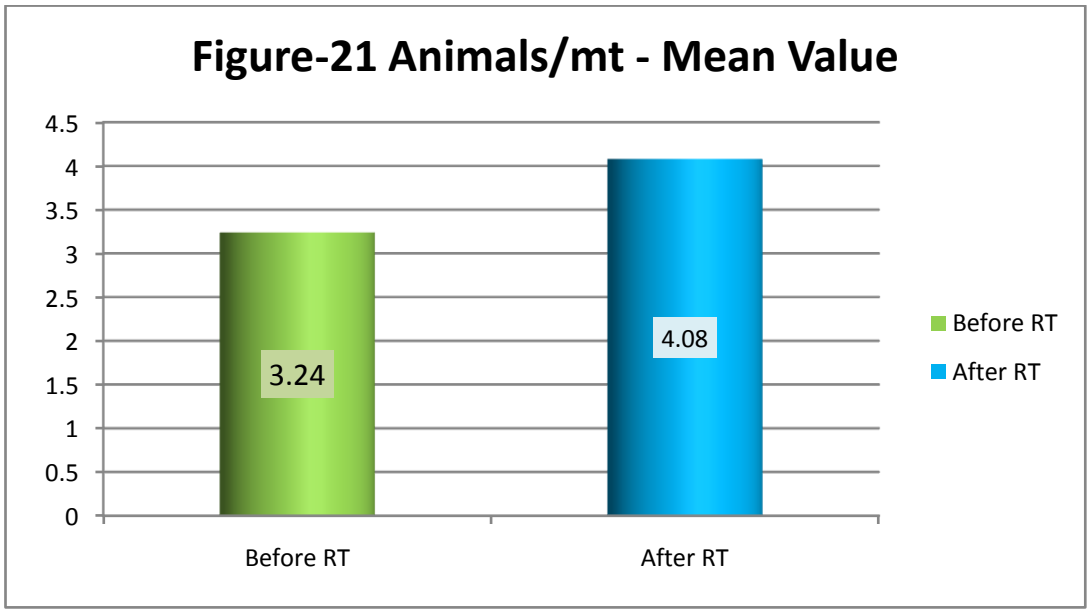


VERBAL FLUENCY TESTING:

21. **Animals/mt before & After RT:**

Animals /mt were tested with each patients and noted significant p value noted after RT. (Table-25and Figure-21).

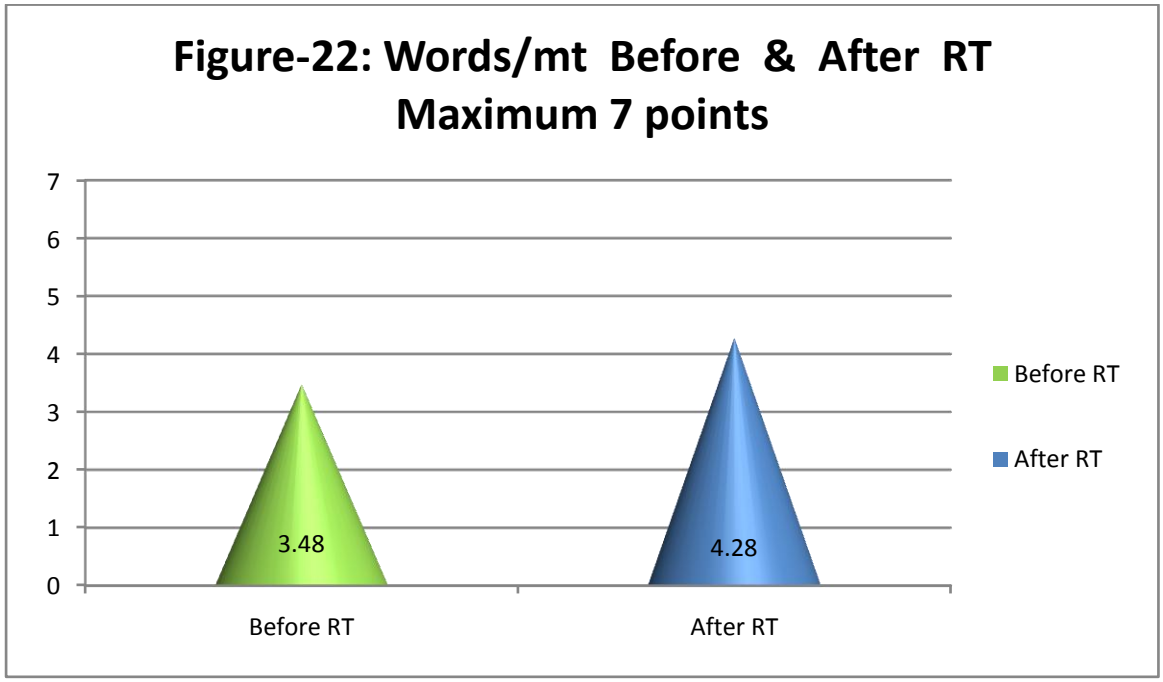
Table-25					
Animals		Mean	N	Std. Deviation	P Value
	Animals/mt before RT max 7 points	3.24	25	.831	**0.000**
	Animals/mt after RT max points 7	4.08	25	1.038	



22. **Words/mt before & After RT:**

FAS test (words/mt) was tested with each patients and noted significant p value noted after RT. (Table-26and Figure-22).

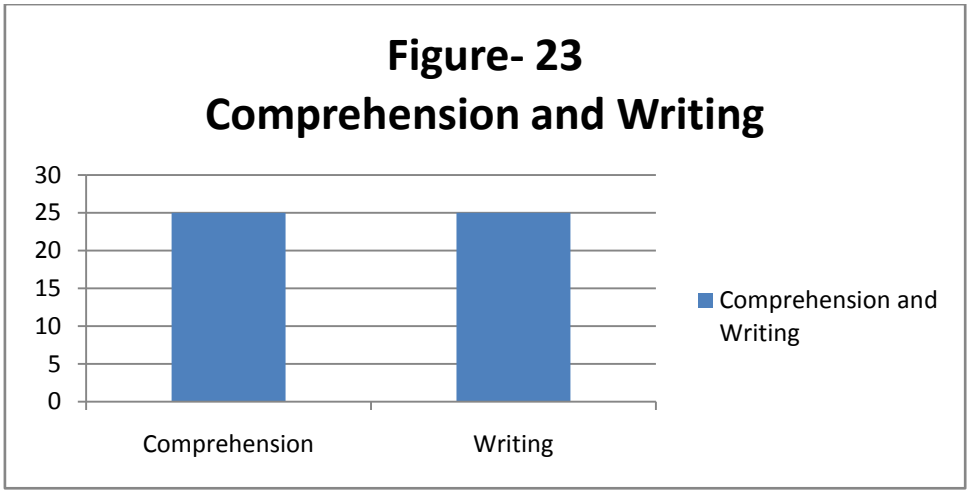
Table-26				
Words	Mean	N	Std. Deviation	P Value
Words/mt before RT max 7 point	3.48	25	.714	**0.000**
Words/mt after RT max 7 points	4.28	25	.980	



22. **Comprehension writing Repetition, Naming, Reading before & After RT:** (Table-27 and Figure-23).

Table-27

			Comprehension writing before RT	Total
			Normal	
Comprehension writing before RT	Normal	Count	25	25
		% within Comprehension writing before RT	100.0%	100.0%
		% within Comprehension writing before RT	100.0%	100.0%
Total		Count	25	25
		% within Comprehension writing before RT	100.0%	100.0%
		% within Comprehension writing before RT	100.0%	100.0%



23. Visuospatial Ability before RT * Visuospatial Ability after RT Crosstabulation

Visuospatial ability before RT and after RT was tested with copying cube, circle, draw a clock face with the numbers on it and there is no significant p value was noted. (Table-28and Figure-24).

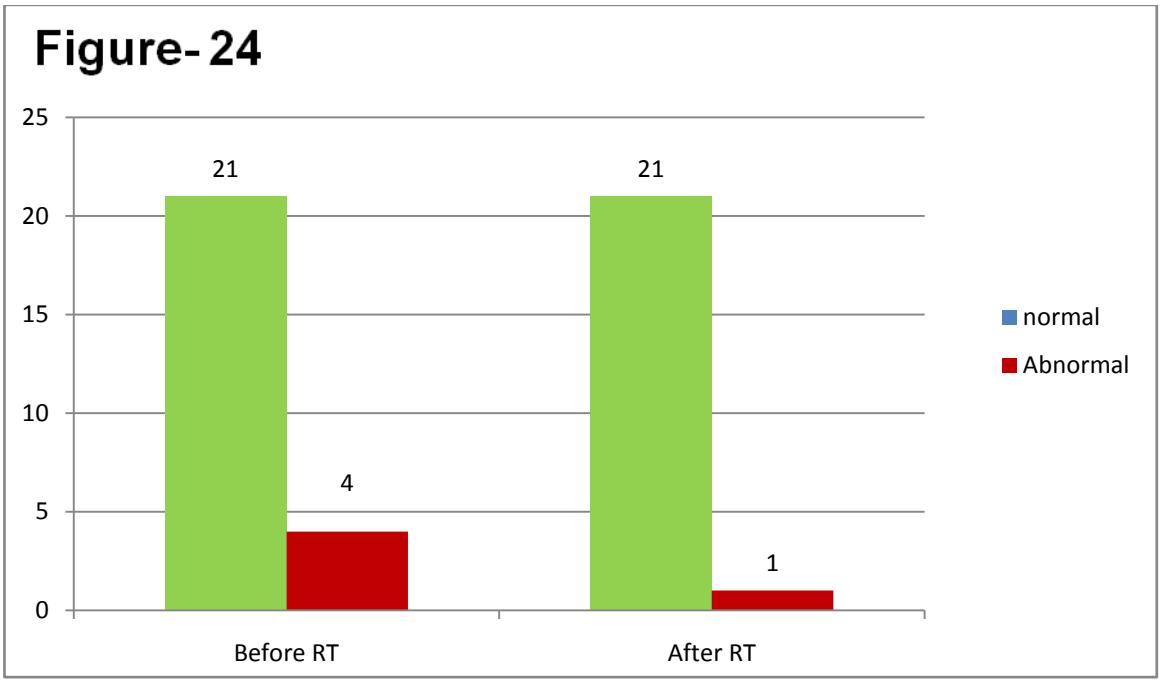


Table-28						
			Visuospatial Ability after RT		Total	P value
			Normal	Abnormal		Pearson Chi-Square
Visuo-spatial Ability before RT	Normal	Count	21	0	21	
		% within Visuospatial Ability before RT	100.0%	.0%	100.0%	.019
		% within Visuospatial Ability after RT	87.5%	.0%	84.0%	
	Abnormal	Count	3	1	4	
		% within Visuospatial Ability before RT	75.0%	25.0%	100.0%	
		% within Visuospatial Ability after RT	12.5%	100.0%	16.0%	
Total		Count	24	1	25	
		% within Visuospatial Ability before RT	96.0%	4.0%	100.0%	
		% within Visuospatial Ability after RT	100.0%	100.0%	100.0%	

24. Perceptual Ability before RT * Perceptual Ability after Identifying letters RT

Perceptual ability was noted with Counting dots, it and there is no significant p value was noted (Table-29 and Figure-25).

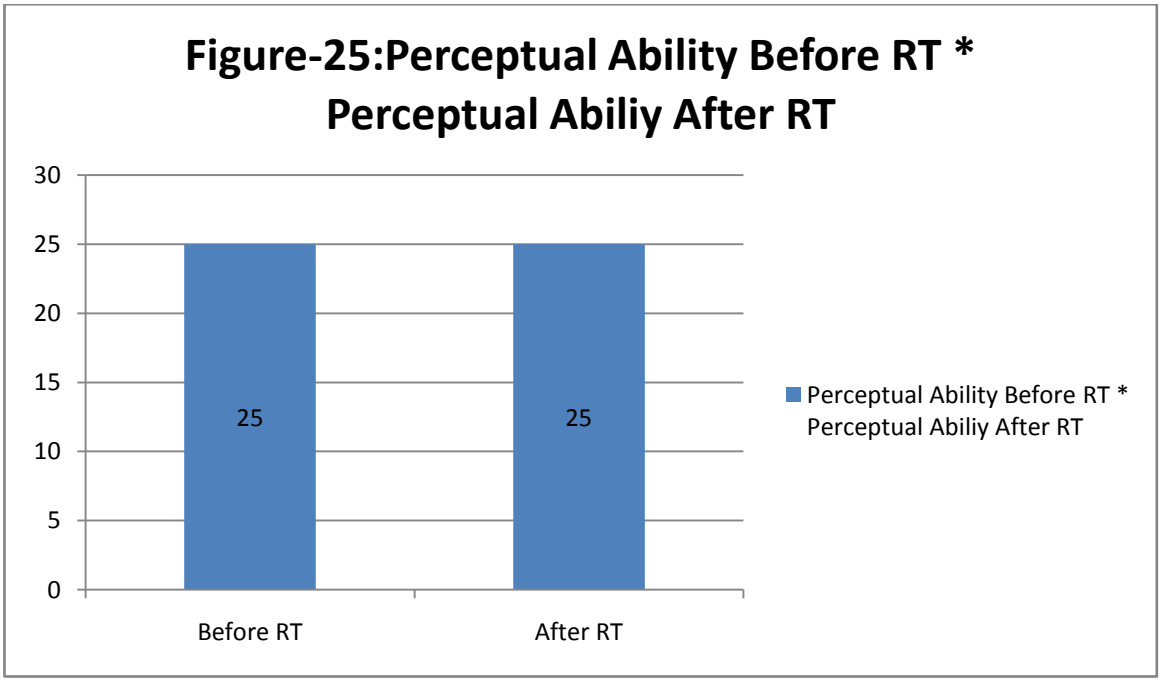


Table-29				
			Perceptual Ability after RT	Total
			Normal	
Perceptual Ability before RT	Normal	Count	25	25
		% within Perceptual Ability before RT	100.0%	100.0%
		% within Perceptual Ability after RT	100.0%	100.0%
Total		Count	25	25
		% within Perceptual Ability before RT	100.0%	100.0%
		% within Perceptual Ability after RT	100.0%	100.0%

25. Copying before RT * Copying after RT table-30 Figure-26

Copying was tested and there is no significant p value noted.

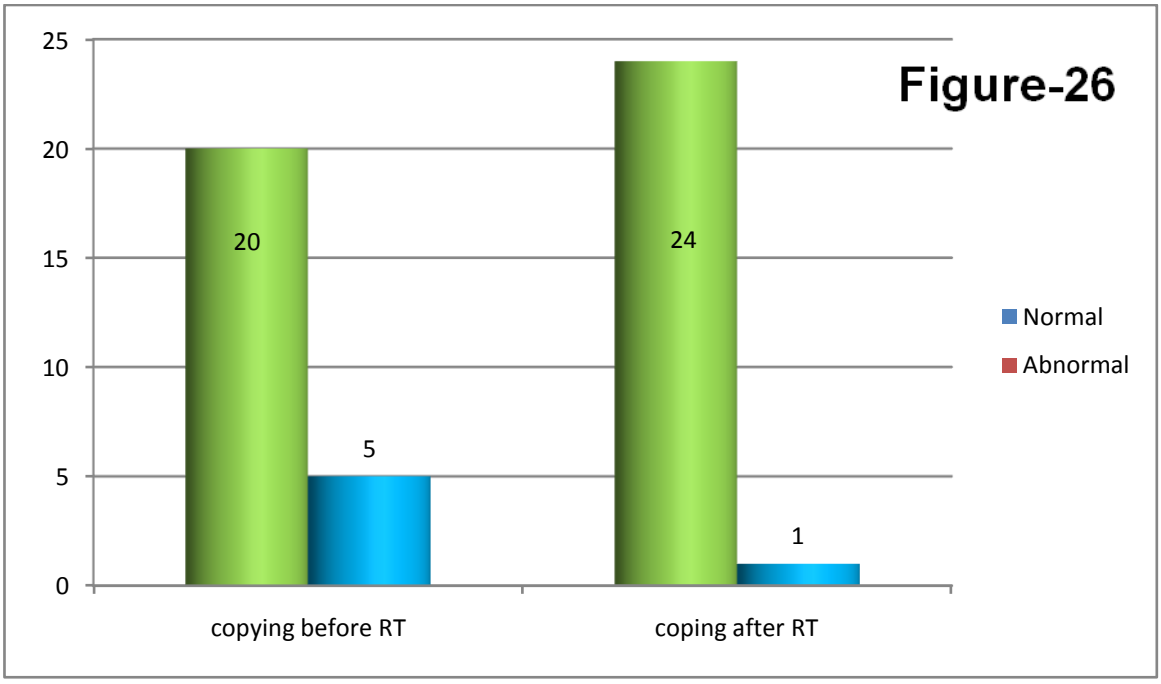


Table-30						
			Copying after RT		Total	P value
			Normal	Abnormal		Pearson Chi-Square
Copying before RT	Normal	Count	20	0		
		% within Copying before RT	100.0%	.0%	100.0%	.041
		% within Copying after RT	83.3%	.0%	80.0%	
	Abnormal	Count	4	1	5	
		% within Copying before RT	80.0%	20.0%	100.0%	
		% within Copying after RT	16.7%	100.0%	20.0%	
Total		Count	24	1	25	
		% within Copying before RT	96.0%	4.0%	100.0%	
		% within Copying after RT	100.0%	100.0%	100.0%	

DISCUSSION

Totally 25 patients were enrolled in this study after getting a written consent to analyze the cognitive status in chronic kidney disease patient before and after renal transplant, (6 to 9 months after renal transplant).

Age Distribution:

The minimum age enrolled was 17 years and maximum age was 49 years. 4 patients were more than 40 years.

Sex Distribution:

In this study, out of 25patients 20 (80%) were males and 5(20%) were females.

Haemoglobin Level:

The mean Hb before RT was 8.44 gms and some of the patients received injection Erythropoietin before surgery. The mean Hb after RT was 11.564 gms and significant p value (0.000) was noted .There is significant increase in haemoglobin level after RT. Usually the Hb improved significantly by 3 months after RT. This corresponds to Iwamoto H [40] (Iwamoto et al., 2014), Nakumura et al study, Montanaro et al study [41].

Blood Urea Level:

The mean blood urea level before RT was 115.60 mgs and the mean blood urea level after RT was 31.60 mgs there is significant notable p value(0.000) .This is correlated with the Reinhardt.w. et al [42] study in post renal transplant that there is significant reduction in blood urea level except in few patients with impaired graft function.

Serum Creatinine:

The mean serum Creatinine level before RT was 8.108 mgs and the mean serum Creatinine level after RT was 1.300mgs and there is significant p value(0.000) was noted. This is correlated with the Reinhardt.w. et al [42] study in post renal transplant there is significant reduction in serum Creatinine level except in few patients with impaired graft function.

Blood pressure:

The mean systolic BP level before RT was 142.40 mm of Hg and the mean systolic BP level after RT was 123.6 mm of Hg and there is significant p value (0.000) noted .The mean diastolic BP level before RT was 90 mm of Hg and the mean diastolic BP level after RT was 80.40 mm of Hg and there is significant p value (0.000) noted. There is significant reduction in the BP

after RT about 30% patient taking regular anti HT drugs even after RT ,this is correlated with previous pilot study(Saxena Anita, Sharma R K etal) [43]

Duration of Dialysis before RT ;

The duration of dialysis varied from 1 month to 10 months depends upon the availability of kidney donor.

Cognitive function compromise has been reported by Techan et al [44] Qurella Chertow, Luan and Yaffe Etal. It depends upon underlying dialysis treatment duration.

Earlier, ESRD patients who underwent haemodialysis procedure continuously may lead to cognitive impairment which is known as Dialysis – Associated Dementia. This was first noted by Alfrey, LeGendre and Kaehny Etal.[45] This dialysis associated dementia could be most often prevented by using water purification technique, thereby preventing aluminium toxicity. (Burn and Bates 1998).[46] .Haemodialysis result in decreased cerebral blood flow and changes in haemotocrit level and other co –morbid Cerebrovascular disease associated with cognitive compromise.(Lass & Colleagues et al 1999).[47] Various studies was performed on attention during dialysis.

COGNITIVE ASSESSMENT:

Executive Function:

Poor executive function has been improved in RT patients when compared to patient on dialysis. This correlates with previous study by Smith, A. (1973) et al [48] and Matthews, C. G., & Klove, H. (1964) [49.] In above study executive function tested by trail making test, simple digit modality test and written test .In both studies, the extent of residual cognition that are present in early CKD is not mentioned which may persist following renal transplantation. . In our study, the executive function has been tested by maze test (Number of error , Time of completion) , Stroop test, Trail making test resulting in statistically significant value noted after renal transplantation by the means of less number of error and less time of completion.

Attention:

Uchida etal [50] studied the performance of attention both before and after successful renal transplant compared to the person on dialysis in 1951 by Uchida – Kraepelin continuous simple addition test[51.] Two longitudinal studies has been conducted for attention by Takuma et al [51] and Krarner et al using an attention task (Trails A) and a cognitive screening measure (MMSE).

The transplant participants were tested prior to RT and 9-19 months after renal transplantation. Post RT performance improved compared to pre RT performance but not at the level of significance.

While these findings provide some support that few domains of cognition (memory &attention) improve from the state of failure to the state of renal compensation (Post RT). The research does not mention to what extent reduced cognitive performance that present in early CKD may persist following RT.

1. Mattews & Klove et al [49] across sectional comparison suggest that improvement of attention and memory but not in executive function following RT. Grivia et al found that there was improvement in attention for RT in comparative dialysis participant (transplant patients showed 32% improvement on simple addition test in second visit) but it was not statistically significant. There is no available data to compare the cognition in early CKD and post RT.
2. In our study attention was tested with digit forward, digit backward, spell backward, simple calculation, Go-no-go test, and Vigilance test. The results showed significant p value (.000) in our study as compared to Uchida etal, Mattews & Klove et al.

Memory:

The important question concerned is that whether the renal transplantation improves one to state of pre-morbid baseline cognition ability. For this question, one must compare the performance of renal RT patients to that of healthy controls.

The griva et al study (2004) [52] showed the memory remains equivocal after RT.Bermond et al study (2005) [53] indicating the poorer memory after RT but lack of study control group. The small size renal RT participants and the control group stated the null difference noted in the study.

Delis –Kaplan [54] executive function system stated that the cognitive function was not found to relate with severity of CKD like Hb level, estimated GFR, the stages of kidney disease and depression was noted.Pliskin, Kiolbasa et al mentioned the co morbid condition like diabetes, HT, CAD and depressive illness may contribute to cognitive worsening in CKD even after the successful RT.

There is general belief that cognitive function will improve after successful RT, but there is no evidence to support this. so, many studies was conducted in children with successful RT like fennel et al Morris et al stated there is no clear evidence finding in children.

Saan& deelman, 1998 [55] evaluate the verbal memory task was compared with normal data and RT patient's worse on verbal memory in RT patients. Bemund et al evaluate the memory in RT patients. The author found that high dose of predinsolone were associated with memory defect like immediate recall, delayed recall, abstract and concrete .This effect particularly due to long term usage of predinsolone leads to increase level of steroids receptors in the hippocampus, this may be related with poor memory function.

In this study there is significant p value noted in recall (three words), Anterograde memory (name and address) , Delayed Recall, verbal fluency (FAS test-words/mt, animals/ mt) word recognition, but the retrograde memory(personal events, family events, name of the prime minister's, the woman who was Prime Minister etc) is not significantly improved.

Language;

The language was tested with Comprehension, writing, repeation; naming, reading perceptual abilities (identifying dots, numbers, and letters).There is no statistically significant changes noted in this study. A visuospatial ability (Circle, Numbers, Hands) was tested .there is significant changes after RT in statistical analysis.

CONCLUSION

1. In this study the cognitive function was assessed in renal transplant receptions before and after surgery with various methods in 25 patients.

2. Among the cognitive function the executive function, Attention task, Anterograde memory, verbal fluency, and word recognition in memory function has been improved after renal transplant.

3. Attention was tested with digit forward, digit backward, spell backward, simple calculation, Go-no-go test, and Vigilance test, the results showed stastically significant p value in our study.

5. In memory function there is significant improvement in recall, anterograde memory, verbal fluency, and word recognition after renal transplant, but there is no significant changes in the retrograde memory.

6. In language domain Comprehension, writing, repeation, naming, reading perceptual abilities (identifying dots, numbers, and letters) there is no statistically significant changes noted before and after renal transplant in this study.

7. There is stastically significant value noted in biochemical parameter like improvement in hemoglobin level, serum Creatinine level decline, blood urea level decline, blood pressure control after the renal transplant.

The sample size was small and needs to study in large groups in various cognitive domains and long term follow-up to determine the cognitive improvement.

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Schindler,

ABBREVIATIONS

RT- renal transplant

CKD- chronic kidney disease

ESRD- end stage renal disease

CAD- coronary Artery disease

MMSE- Mini Mental State Examination

ADAS-Alzheimer's Disease Cooperative Study

GFR-glomerular filtration rate

ACE-Angiotensin Converting Enzyme

WMLs-white matter lesions (WMLs)

SLB-silent brain infarcts

MRI-Magnetic resonance imaging

To study and analyses the cognitive profile in chronic kidney disease patient before and After renal transplant''.

Name: Date:

Age/Sex: OP/IP No:

Weight: MIN No:

Occupation: DOA;

Mother Tongue:

Income: DOS;

DOD;

Address: donor 1.live;

a. Relative A. relative

Phone number: B. Spouse

Educational status: 2.Cadaver

Biopsy report;

Drug protocol;

Clinical Examination:

1. Mini Mental State Examination
2. Detailed Lobar function
3. Addenbrooke's Cognitive Examination
4. Wescthler Memory Scale
5. ADAS- Cognitive Behavior

S.No	Name	Age	Sex	Donor - Cadaver (1) Live (0)	Haemoglobin(%) before RT	Heamogloblin(%) after RT	Blood urea before RTmgs	Blood urea after RT(mgs)	Sr.creatinine before RT	Sr.creatinine after RT	Systolic BP mm of Hg before RT	Systolic BP after RT mm of HG	Diastolic BP mm of Hg before RT	Diastolic BP mm of Hg after RT
1	Jayalakshmi	22	F	Live (1)	8.8	12.3	188	48	8.8	1.7	160	120	100	80
2	Elumalai	36	M	Live (1)	8.6	11,2	110	25	6.7	1.2	170	140	100	90
3	DR.Pradeepa	29	F	Live (1)	7.8	11.3	128	28	6.9	1.3	150	140	100	80
4	Namas Khan	26	M	Cadaver (0)	8.6	11.3	72	35	8.6	1.8	150	120	90	80
5	Munusamy	26	M	Cadaver (0)	8.9	12.6	110	28	5.6	0.8	120	120	80	80
6	Sethu	47	M	Live (1)	9.2	10.6	98	28	11	0.9	150	120	90	80
7	Venkatesan	36	M	Live(1)	8.6	12.3	118	29	6.8	1	150	140	100	90
8	Kamaledeen	34	M	Cadaver (0)	7.8	12.4	110	30	12	1.3	150	140	80	80
9	Muniappan	29	M	Live (1)	8.9	11.4	106	46	5.6	1.3	20	120	80	80
10	Davidraj	23	M	Live (1)	8.6	11.4	78	46	5.8	2.5	120	120	80	80
11	Kasiyal keliyan	43	M	Cadaver (0)	8.7	12.3	110	36	11	1.2	150	140	100	90
12	Kitteswari	33	F	Cadaver (0)	8.2	11.2	110	29	8.8	1.2	140	120	90	80
13	Venkatraman	36	M	Live (1)	8.3	11.2	98	32	8.8	1.3	150	130	100	90
14	Raj	34	M	Cadaver (0)	8.2	12.3	112	34	7.6	1.4	180	130	90	70
15	Venkatbabu	27	M	Live (1)	8.2	12.3	128	28	7.8	1.2	170	120	80	70
16	Ramesh	27	M	Cadaver(0)	8.4	10.8	122	32	6.8	1.4	120	110	80	70
17	Velmurugan	35	M	Live (1)	8.2	10.3	110	28	9.8	1.3	120	110	80	80
18	Elongovan	35	M	Cadaver(0)	8.4	10.9	112	24	6.8	1.3	160	110	80	80
19	Munusamy	31	M	Cadaver(0)	8.4	10.8	126	28	8.9	1.2	120	110	80	80
20	Shiek farid	17	M	Live (1)	8.2	11.3	112	26	7.8	1.2	170	110	100	80
21	Srimathi	23	F	Live (1)	8.6	10.4	134	28	7.8	1.2	120	120	80	80
22	Shanthi	32	F	Live (1)	8.2	10.3	112	32	6.8	1.2	160	120	100	80
23	Kamatchi	49	F	Cadaver (0)	8.2	12.4	124	28	10.8	1.2	150	120	90	80
24	Sekar	45	M	Live (1)	8.4	12.4	118	28	6.8	1.1	150	120	100	80
25	Nagaraj	38	M	Cadaver (0)	8.6	12.4	144	34	8.8	1.3	160	140	100	80

							Executive Function			
< 3 months duration of dialysis	>3- 6 months duration of dialysis	> 6 months duration of dialysis	MMSE before RT maximum score 30	MMSE after RT maximum score 30	Attention & Orientation - (15 pts) before RT	Attention & Orientation - (15 pts) after RT	Number of Errors before RT	Number of Errors after RT	Time at completion in sec before RT	Time of completion in sec after RT
-	Y	-	28	29	14	14	0	0	10	8
-	Y	-	23	26	14	14	0	0	12	9
Y	-	-	30	30	15	15	0	0	6	4
Y	_	_	28	28	14	15	0	0	10	8
Y	_	_	27	27	14	14	0	0	12	10
Y	_	_	27	27	14	14	0	0	11	10
-	Y	-	29	29	14	14	0	0	10	9
_	y	_	26	25	13	14	0	0	8	10
y	_	_	26	26	13	13	0	0	12	10
y	_	_	27	28	14	14	0	0	12	11
_	y	_	27	27	14	14	1	0	12	10
_	_	y	27	27	14	14	0	0	12	11
_	y	_	28	28	14	14	0	0	10	9
_	_	y	28	28	13	14	0	0	12	9
_	y	_	28	28	13	13	0	0	12	9
	y	_	28	28	13	13	0	0	12	9
y	_	_	28	28	13	13	0	0	12	8
_	y	_	28	28	13	14	1	0	10	8
_	y	_	28	28	13	14	1	0	10	8
y	_	_	28	28	13	13	0	0	10	8
y	_	_	28	28	13	14	0	0	12	8
y	_	_	28	28	13	14	0	0	12	9
_	y	_	28	28	13	14	0	0	12	9
y	_	_	27	28	13	14	0	0	12	8
y	_	_	27	28	13	14	0	0	12	9

								Memory							
Registration Before & after RT	Attention Before RT	Attentionafter RT	Calculation before RT	Calculation after RT	Constructional Praxis before RT	Constructional Praxis after RT	Ideational Praxis before &after RT	Recall before RT (max 3 points)	Recall after RT (max 3 points)	Anterograde (max points = 7)before RT	Anterograde (max points = 7) after RT	Delayed Recall (max 7 points) before RT	Delayed recall after RT	Retrograde (max 4 points) before RT	Retrograde (max 4 points) after RT
3	5	5	5	5	N	N	N	3	3	5	6	5	5	2	2
3	5	5	5	5	N	N	N	3	3	4	5	4	4	1	2
3	5	5	5	5	N	N	N	3	3	7	7	7	7	4	4
3	5	5	5	5	N	N	N	3	3	5	5	3	4	3	3
3	5	5	5	5	N	N	N	2	3	4	5	3	5	2	2
3	5	5	5	5	N	N	N	1	2	4	4	4	4	2	2
3	5	5	5	5	A	A	N	1	2	3	4	3	3	1	2
3	5	5	5	5	N	N	N	3	3	4	4	3	3	2	2
3	5	5	5	5	A	N	N	2	2	4	4	3	4	2	2
3	5	5	5	4	A	A	N	3	3	4	5	3	3	2	2
3	5	5	5	5	N	N	N	2	2	4	4	3	3	3	3
3	5	5	_	_	N	N	N	2	2	4	4	3	4	2	3
3	5	5	5	5	N	N	N	3	3	4	4	3	4	3	3
3	5	5	5	5	N	N	N	2	3	3	4	3	4	3	3
3	3	5	5	5	N	N	N	3	3	4	4	3	4	3	3
3	5	5	5	5	A	N	N	2	3	4	4	3	4	3	3
3	5	5	5	5	N	N	N	3	3	4	5	3	3	3	3
3	5	5	5	5	N	N	N	2	3	4	5	3	3	3	3
3	5	5	5	5	N	N	N	3	3	4	5	3	3	3	3
3	5	5	5	5	N	N	N	2	3	4	5	3	3	3	3
3	5	5	5	5	N	N	N	3	3	4	5	3	4	4	4
3	5	5	5	5	A	A	N	3	3	4	4	3	4	4	4
3	5	5	5	5	N	N	N	3	3	4	4	3	4	4	4
3	4	5	4	5	N	N	N	2	3	4	4	3	3	3	4
3	5	5	4	4	N	N	N	2	3	4	4	3	3	3	4

		Verbal Fluency							Language									
Word Recognition before RT	Word Recognition after RT	Animals/mt before RT (max 7 points)	Animals/mt after(RT max points 7)	Words/mt before RT (max 7 point)	Words/mt after RT (max 7 points)	Comprehension before RT after RT	Writing before RT after RT	Repetition before RT &after RT	Naming before RT (max 10 points)	Naming after RT (max 10 points)	Reading before RT	Reading after RT	Visuospatial abilities before RT	Visuospatial abilities after RT	Perceptual ability before RT	Perceptual ability after RT	Copying before RT	Copying after RT
7	8	6	7	4	6	N	N	N	7	8	N	N	N	N	N	N	N	N
6	7	3	5	3	4	N	N	N	8	8	N	N	A	N	N	N	A	A
10	10	6	7	6	7	N	N	N	10	10	N	N	N	N	N	N	N	N
5	6	3	4	3	4	N	N	N	5	5	N	N	N	N	N	N	N	N
6	7	3	5	4	5	N	N	N	5	6	N	N	N	N	N	N	A	N
6	7	3	4	4	4	N	N	N	6	6	N	N	N	N	N	N	N	N
5	6	3	4	3	4	N	N	N	5	5	N	N	A	N	N	N	N	N
6	6	3	3	3	4	N	N	N	6	6	N	N	N	N	N	N	N	N
6	6	3	3	3	4	N	N	N	6	6	N	N	A	A	N	N	A	N
6	6	3	3	3	4	N	N	N	6	6	N	N	N	N	N	N	A	N
6	7	3	4	3	3	N	N	N	6	6	N	N	N	N	N	N	N	N
5	5	3	3	3	3	N	_	N	6	6	_	_	A	N	N	N	A	N
5	5	3	3	3	3	N	N	N	6	6	_	_	N	N	N	N	N	N
5	5	3	4	3	4	N	N	N	6	6	N	N	N	N	N	N	N	N
5	5	3	4	3	3	N	N	N	6	6	N	N	N	N	N	N	N	N
5	5	3	4	3	3	N	N	N	6	6	N	N	N	N	N	N	N	N
5	5	3	4	3	4	N	N	N	6	6	N	N	N	N	N	N	N	N
6	6	3	4	3	4	N	N	N	6	6	N	N	N	N	N	N	N	N
6	6	3	4	3	4	N	N	N	6	7	N	N	N	N	N	N	N	N
6	6	3	4	4	5	N	N	N	6	7	N	N	N	N	N	N	N	N
6	6	3	3	4	5	N	N	N	6	7	N	N	N	N	N	N	N	N
6	7	3	4	4	5	N	N	N	6	6	N	N	N	N	N	N	N	N
6	7	3	4	4	5	N	N	N	6	7	N	N	N	N	N	N	N	N
6	7	3	4	4	5	N	N	N	6	7	N	N	N	N	N	N	N	N
6	6	3	4	4	5	N	N	N	6	7	N	N	N	N	N	N	N	N